Comparison of Surgical Site Infection between Delayed Primary versus Primary Wound Closure in Complicated Appendicitis; A Multicenter Randomized Controlled Trial
Introduction

• Tubular structure
• Appendicitis is the most common surgical condition
• Pathophysiology: Luminal obstruction
Appendicitis
• Appendectomy: standard treatment
• Through right lower quadrant incision
• McBurney’s point
Appendicitis Classification
a) Inflamed b) gangrenous c) perforation (ruptured) d) fecolith
• Complicated appendicitis = gangrenous and ruptured
  • Associated with more complications
Surgical site infection: most common complication after appendectomy
  - Esp. in complicated appendicitis
  - Affect both patients and healthcare provider

In Thailand: about 20,000 ruptured appendicitis per year
  - Rate of wound infection: 10-50%
    - More nursing care, pain, length of stay, decrease quality of life
    - Increase both direct and indirect cost
  - High impact to our society
Pathophysiology

1. Microbe related: degree of contamination, virulence of bacteria
2. Host defense mechanism: immunocompromised
3. Operative related: prolonged hospital stay, use of drain
Type of wound closure

Primary closure (PC)
  • Closed wound immediately after operation

Delayed primary closure (DPC)
  • Closed 3-7 day after operation with proper wound care

Secondary intention or closure
  • Dressing until wound completely healed
Delayed Primary Wound Closure (DPC)

- Introduce since World War I in traumatic wound
- In 24-48 hr, epithelialization of primary closure dirty incisions
  - Trap bacteria, exudates, clots, and debris

**Delayed primary closure (DPC)**

- Effect in reducing the number of bacteria contamination and colonizing the incision
- Increase local wound resistance, tissue oxygenation, wound blood supply within 3-5 postoperative day
- Incisions closed within 5 days: same strength as primary closure

*Plast Reconstruc Surg 1971; 48: 358-360*
Cons of DPC

- Daily wound dressing
- Necessitate of resuturing
- ? Increase pain, length of stay
- Increase cost of treatment

- Considered as invasive intervention
Good research questions

From your practice ...., relevant question ...

And you want to know the truth

Then, you want to prove it ...

It will benefit to other patients

Find previous literature
A systematic review and meta-analysis of randomised controlled trials of delayed primary wound closure in contaminated abdominal wounds

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Systematic review and meta-analysis

Figure 1 Studies selection flow.
### Systematic review and meta-analysis

**RR 0.89 (0.46, 1.73)**  
*I² = 62%*  
Uncertainty  
High risk of bias (poor randomization)

**Figure 2 Forest plot of superficial surgical site infection between primary and delayed primary wound closure according to type of patients.** CI, confidence interval; DPC, delayed primary closure; RR, risk ratio.
• **Wound infection**
  - Increase wound dehiscence
  - Increase incisional hernia
  - Increase cost

• **DPC**
  - Increase pain, length of stay, decrease quality of life
  - Study from Canada in 1991: DPC increased cost of up to $400 (1,000 Bahts at that time)

(J Pediatr Surg 1991;26:1362-5)
Research Question

Does delayed primary wound closure after appendectomy in adults with complicated appendicitis with right lower quadrant wound incision reduce postoperative superficial incisional surgical site infection compare to primary wound closure?
Research objectives

**Primary Objective**

To compare the rate of postoperative superficial incisional surgical site infection in complicated appendicitis between primary and delayed primary wound closure.

**Secondary Objectives**

1) To compare postoperative pain scores at days 1 and 3 after appendectomy between primary and delayed primary wound closure.

2) To compare quality of life at postoperative days 3 and 30 after appendectomy between primary and delayed primary wound closure.

3) To do cost-utility analysis between primary and delayed primary closure in complicated appendicitis.
All clinical trials should be registered at or before the time of first patient enrollment. For consideration of publication.
Clinical trial

What is clinical trial?
- Prospective study
- Assign intervention
- With or without comparison or control group

Intervention-----------------------------Outcomes

- Drugs
- Surgical procedures
- Devices,
- Behavioural treatment
- Education programs, dietary interventions, Quality improvement interventions, Process-of-care changes

- Biomedical or health-related measures obtained in patients or participants

Including pharmacokinetic and adverse events
Methodology

Good research questions
And equipoise

• Negotiate and convince collaborator
• It will work if you believe in that too (have faith) (relevant question + equipoise + good review data)
• This will keep your collaborator randomizing patients for you
• Other benefit ---- side paper, money ???
• Not too complicate research
Inclusion criteria

• Age > 18 year + have appendectomy with right lower quadrant incision

Operative criteria for complicated appendicitis

Gangrenous appendicitis
- Erythematous or swelling of appendix and
- Appearance of necrotic wall (dark, grayish color)

Ruptured appendicitis
- Erythematous or swelling of appendix and
- Appearance of hole in an appendix or
- Rupture of appendix during a procedure
- Appearance of frank pus
Exclusion criteria

Immunocompromised hosts

• AIDS
• History of end-stage renal disease (ESRD)
• History of autoimmune disease (SLE)
• Taking immunosuppressive agents (prednisolone, methotrexate, cyclophosphamide, azathioprine, mercaptopurine, anthracycline, mitomycin, Ciclosporin, Tacrolimus)
• Cirrhosis with ascites
• Morbid obesity (BMI > 40 kg/m2)
Randomization

- Ratio 1:1
- **Stratified block randomization based on study site**
- Vary block size of 4 to 6
- Sequence generation: independent statistician
- Allocation concealment: sequential sealed opaque envelope
  - Open: met intraoperative criteria
  - **Before skin closure**
Blinding

- Primary outcome
  - Not blinded
  - Standard operative procedure for measure outcome

- Research assistant
  - Secondary outcomes (pain, recovery time, quality of life, cost)
  - blinded
Co-intervention

• Perioperative antibiotics
• Postoperative pain control
• Wound dressing and care

• Important co-intervention = major confounder to the outcomes
• Meeting and consensus between all collaborator
Outcomes

- Superficial surgical site infection
  - CDC criteria
- Postoperative pain: VAS (100 mm scale)
- Recovery time
  - Times to return to normal activities (day)
  - Times to return to work (day)
- Quality of life
  - EQ5D (5 scale) ------ convert to utility scores
- Costs
  - Direct medical costs: assume equal except cost of wound care (dressing and resuture)
  - Direct non-medical cost and indirect cost: interview
Patient’s flow

Eligible patients

Inclusion criteria

Informed by physician

Non-participants

Participants

Consent form
Participants → Operation → Randomization → Operative criteria

Outcome assessment

- DPC
  - Day 1: Pain; n =
  - Day 3: Pain, EQ5D; n =
  - Before discharge: SSI; n =
  - 1 wk FU: SSI; n =
  - 1 mo FU: EQ5D, SSI; n =

- PC
  - Day 1: Pain; n =
  - Day 3: Pain, EQ5D; n =
  - Before discharge: SSI; n =
  - 1 wk FU: SSI; n =
  - 1 mo FU: EQ5D, SSI; n =

Intention to treat Analysis
Sample size estimation

- Pooled rate of SSI in DPC = 29.5 (95%CI: 14.8, 44.2)
- Type I error = 0.05
- Power = 0.8
- Ratio 1:1
- Test for difference (two-sided)
- Size of detectable = 10%
- 285 / group -------- 570 + 5% loss FU
  -------- 600
Data analysis

• Intention to treat analysis

• Primary outcomes
  • Binary regression analysis with or without adjusted variable
  • Protocol violation: Per-protocol, as-treated, counterfactual
  • Imputed data

• Secondary outcomes
  • Mixed linear regression model

• Cost-utility analysis
  • Incremental cost-effectiveness ratio (ICER)
Results

- 607 patients
  - 126 Thammasat University
  - 92 Ramathibodi
  - 117 Chonburi
  - 30 Pathum tani
  - 170 Lampang
  - 72 Surin
Consort flow diagram

Figure 1. Consort flow diagram
Think about real situation to prevent possible risk of error

Frequent monitoring --- rapid active action to the problem

Rapid input of data when it is collected and checked as soon as possible
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>DPC (n = 304)</th>
<th>PC (n = 303)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>46 (18.0)</td>
<td>45 (18.1)</td>
</tr>
<tr>
<td>Gender, number (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>155 (51)</td>
<td>169 (56)</td>
</tr>
<tr>
<td>Female</td>
<td>149 (49)</td>
<td>134 (44)</td>
</tr>
<tr>
<td>BMI, kg/m², mean (SD)</td>
<td>23.4 (4.31)</td>
<td>23.4 (4.34)</td>
</tr>
<tr>
<td>Smoking, number (%)</td>
<td>45 (15)</td>
<td>51 (17)</td>
</tr>
<tr>
<td>ASA classification, number (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I + II</td>
<td>266 (89)</td>
<td>257 (85)</td>
</tr>
<tr>
<td>Class III + IV</td>
<td>34 (11)</td>
<td>44 (15)</td>
</tr>
<tr>
<td>Diabetes, number (%)</td>
<td>31 (10.3)</td>
<td>20 (6.7)</td>
</tr>
<tr>
<td>Hypertension, number (%)</td>
<td>55 (18.2)</td>
<td>60 (20)</td>
</tr>
<tr>
<td>Symptom onset, hours, mean (SD)</td>
<td>24 (15, 18)</td>
<td>24 (14, 18)</td>
</tr>
<tr>
<td>White blood cell count, cell/mm³, mean (SD)</td>
<td>15561 (4965)</td>
<td>15790 (4979)</td>
</tr>
<tr>
<td>Body temperature, Celsius, mean (SD)</td>
<td>37.7 (1.0)</td>
<td>37.7 (1.1)</td>
</tr>
<tr>
<td>Fever, number (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 37.8 Celsius</td>
<td>142 (47)</td>
<td>148 (49)</td>
</tr>
<tr>
<td>&lt; 37.8 Celsius</td>
<td>159 (53)</td>
<td>154 (51)</td>
</tr>
<tr>
<td>Preoperative utility, median (IQR)</td>
<td>0.68 (0.34, 0.80)</td>
<td>0.68 (0.34, 0.80)</td>
</tr>
<tr>
<td>Operative time, minutes, median (IQR)</td>
<td>47 (14, 74)</td>
<td>51 (18, 78)</td>
</tr>
<tr>
<td>Operative time classification, number (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 75 percentile (&lt; 77 minutes)</td>
<td>232 (77)</td>
<td>222 (74)</td>
</tr>
<tr>
<td>&gt; 75 percentile (≥ 77 minutes)</td>
<td>68 (23)</td>
<td>80 (26)</td>
</tr>
</tbody>
</table>
Baseline characteristics (2)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>DPC (n = 304)</th>
<th>PC (n = 303)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Used of drain, number (%)</td>
<td>62 (20.6)</td>
<td>58 (19.2)</td>
</tr>
<tr>
<td>Severity, number (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gangrene</td>
<td>76 (25)</td>
<td>72 (24)</td>
</tr>
<tr>
<td>Ruptured</td>
<td>228 (75)</td>
<td>231 (76)</td>
</tr>
<tr>
<td>Intraoperative rupture</td>
<td>23 (7.6)</td>
<td>20 (6.6)</td>
</tr>
<tr>
<td>Visible wound contamination, number (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exudative fluid</td>
<td>81 (27)</td>
<td>87 (29)</td>
</tr>
<tr>
<td>Pus</td>
<td>118 (39)</td>
<td>108 (36)</td>
</tr>
<tr>
<td>Feculent material</td>
<td>38 (13)</td>
<td>38 (13)</td>
</tr>
</tbody>
</table>
• 9 miss outcomes
• 52 superficial SSIs
• 8.7% (95%CI: 6.7, 11.2)
• 88% diagnosed in 1 week FU, 12% at 1 month FU
<table>
<thead>
<tr>
<th>Approach</th>
<th>DPC</th>
<th>PC</th>
<th>RR (95%CI)</th>
<th>RD (95%CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>300</td>
<td>298</td>
<td>0.74 (0.44, 1.25)</td>
<td>-0.026 (-0.071, 0.019)</td>
<td>0.258</td>
</tr>
<tr>
<td>Rate (%, 95%CI)</td>
<td>10 (6.6, 13.3)</td>
<td>7.3 (4.4, 10.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>294</td>
<td>289</td>
<td>0.80 (0.47, 1.36)</td>
<td>-0.019 (-0.065, 0.026)</td>
<td>0.411</td>
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<tr>
<td>Rate (%, 95%CI)</td>
<td>9.5 (6.2, 12.9)</td>
<td>7.6 (4.6, 10.7)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>AT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>303</td>
<td>295</td>
<td>0.88 (0.52, 1.48)</td>
<td>-0.011 (-0.56, 0.034)</td>
<td>0.632</td>
</tr>
<tr>
<td>Rate (%, 95%CI)</td>
<td>9.2 (5.9, 12.5)</td>
<td>8.1 (5.0, 11.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>294</td>
<td>293</td>
<td>0.72 (0.32, 1.12)</td>
<td>-0.028 (-0.076, 0.019)</td>
<td>0.243</td>
</tr>
<tr>
<td>Rate (%, 95%CI)</td>
<td>10.1 (6.6, 13.8)</td>
<td>7.4 (4.4, 10.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV (with adjusted variables)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>276</td>
<td>282</td>
<td>0.66 (0.30, 1.01)</td>
<td>-0.036 (-0.083, 0.011)</td>
<td>0.118</td>
</tr>
<tr>
<td>Rate (%, 95%CI)</td>
<td>10.7 (7.0, 14.1)</td>
<td>6.9 (4.1, 9.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DPC --- 10 %
PC --- 7.3%
RR = 0.74 (0.44, 1.25)
Discussion

• Rate of SSI between DPC and PC
  • Not different
• Length of stay, recovery time, postoperative pain, and QoL
  • Not different
• Less cost in PC : ~ 2100 Baht/case
Discussion

- Approaches
  - Increase robustness of the results
  - Different approaches

- Per-protocol: selection bias
- As-treated: observational studies (randomisation broke)
- Counterfactual: complier average causal effect (CACE)

- ITT: policy maker (equal proportion of nonadherence in studies and in population), clinical practice guideline
- CACE: clinician recommendation for complied patients
Cost-effectiveness

- ICER = \([\text{cost}(A) - \text{cost}(B)] / [\text{QALY}(A) - \text{QALY}(B)]\)

- With increase cost with no benefit and QALY gain
- Not cost-effectiveness (dominated)
Impact of studies

- PC saves 2083 Baht/case over DPC
- 65,729,098 population in mid 2015
- Estimated incidence of appendicitis of 14/10000 pop/year = 92020 appendectomy/year
- With 18.2% = complicated appendicitis
  - 16,748 complicated appendicitis / year
- Apply PC in every case: saves 34,886,084 Baht /year
PC is not different comparing to DPC in adults with complicated appendicitis (i.e. gangrenous and ruptured) with lower costs.
Thank you

- Team approach
- Good mentor
- Good collaborator
- Your mind --- face the problem, don’t give up, be patience, happy with it --- successful
<table>
<thead>
<tr>
<th>Dimension</th>
<th>UK</th>
<th>Thai</th>
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</thead>
<tbody>
<tr>
<td>Constant</td>
<td>0.081</td>
<td>0.202</td>
</tr>
<tr>
<td>Mobility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Level 2</td>
<td>0.069</td>
<td>0.121</td>
</tr>
<tr>
<td>Level 3</td>
<td>0.314</td>
<td>0.432</td>
</tr>
<tr>
<td>Self care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Level 2</td>
<td>0.104</td>
<td>0.121</td>
</tr>
<tr>
<td>Level 3</td>
<td>0.214</td>
<td>0.242</td>
</tr>
<tr>
<td>Usual activities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Level 2</td>
<td>0.036</td>
<td>0.059</td>
</tr>
<tr>
<td>Level 3</td>
<td>0.094</td>
<td>0.118</td>
</tr>
<tr>
<td>Pain/discomfort</td>
<td></td>
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</tr>
<tr>
<td>Level 1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Level 2</td>
<td>0.123</td>
<td>0.072</td>
</tr>
<tr>
<td>Level 3</td>
<td>0.386</td>
<td>0.209</td>
</tr>
<tr>
<td>Anxiety/depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Level 2</td>
<td>0.071</td>
<td>0.032</td>
</tr>
<tr>
<td>Level 3</td>
<td>0.236</td>
<td>0.11</td>
</tr>
<tr>
<td>N3</td>
<td>0.269</td>
<td>0.139</td>
</tr>
</tbody>
</table>
• Direct cost
  • Direct medical costs
    • Cost of goods and services that are directly provided by the health care system
    • Hospital days, drugs, home nursing
  • Direct non-medical costs
    • Costs of goods and services used for health care that are not directly provided by the health care system
    • Informal care, transportation
• Indirect cost
  • Indirect non-medical costs
    • The value of production loss due to illness or treatment
    • Income lost from sick-leaved
CDC criteria for superficial SSI

• Infection occurs within **30 days** after the operative procedure and
• Involves **only skin and subcutaneous tissue** of the incision and
• One of the following
  - Purulent drainage from the superficial incision.
  - Organism isolated from an aseptically obtained culture of fluid or tissue from the superficial incision.
  - At least one of the following signs or symptoms: pain or tenderness; localized swelling, redness, or heat **And** the superficial incision is deliberately opened by surgeon (A negative culture does not meet this criterion)